JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Neonatal Pain Management Clinical Pathway

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Rationale

A neonatal pain care plan includes individualized non-pharmacological pain methods in conjunction with pharmacological pain methods is essential for a comprehensive pain care plan to utilize before, during, and after stress and pain in a neonate.

The non-pharmacological approach is the first line of preventing and alleviating pain. It encompasses a wide variety of interventions that include and are not limited to: infant positioning, skin-to-skin, four-handed and hand hug care, stress reduction, Breastfeeding, non-nutritive sucking and the implementation of behaviorally appropriate interventions. Please refer to the Neuroprotective Care of the NICU infant" on connect for further guidance and to the "non-Pharmacologic pain interventions pathway" below (1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 15, 16,17).

Background / Published Data and Levels of Evidence

The knowledge of pain in neonates has increased dramatically in the past three decades. It has been well established that newborns can detect, process, and respond to painful stimuli. Preterm infants are even more hypersensitive to pain and at greater risk for pain due to immature pain inhibition mechanisms at birth. Gaps exist in knowledge, evidence, and practice in neonatal pain assessment and management, which may lead to challenges in managing the pain.

Pain modulation and prevention is essential to optimal neurodevelopmental outcomes of infants (5). Parents of neonates expect the prevention of pain in the healthcare plan (5). Nonpharmacologic inventions are important methods that can reduce neonatal pain by initiating inhibitory pathways or hindering nociceptive communication (7). Utilizing non-pharmacological pain strategies within the pain management care plan is crucial for reducing neonatal pain.

Careful consideration must be taken in administering analgesics to neonates and infants in the NICU. This is due in part to the difficulty of pain assessment, variability in individual metabolisms, neurodevelopment and drug clearance rates; all of which can lead to adverse events and side effects. Pharmacological therapy should be administered in a stepwise approach. The type of pain that the neonate is experiencing (i.e., procedural vs. disease process) will determine the type of analgesia best suited.

Clinical Management

- A pain management plan should support the infant before, during, and after pain. In all pain management plans, non-pharmacological pain management methods should be used in conjunction with pharmacological pain management.
    - Non- pharmacological methods include planning, assessment, and coordination with all care team members (see non-pharmacological pain interventions pathway)
        - Positioning
        - Skin-to-skin
        - Four-handed care / hand hug
        - Neonatal stress
        - Breastfeeding
        - Non-nutritive sucking

- Treatment of Procedural Pain
    - The ideal analgesic for procedural pain must have:
        - A rapid onset and short duration of action with minimal impact on respiratory mechanics.
        - Has not been documented to positively impact oxygen saturation, cerebral blood flow or tissue oxygenation, or neural activity of nociception-evoked circuits.
    - **Oral Sucrose**
        - Used in infants up to 4 months of age
        - Offer a pacifier to the infant, with 0.5 mL sucrose, 2 minutes before beginning the procedure to encourage non-nutritive sucking.
        - May repeat dose 2 times during procedure, but no more than 8 doses should be administered per 24 hours.
            - Gestational specific max dose per administration
                - GA 27 to 31 weeks: 0.5 mL
                - GA 32-36 weeks: 1 mL
                - GA ≥37 weeks: 2 mL
        - Contraindications
            - Patients with irritability or for ongoing pain relief
            - Known, suspected, or at high risk for necrotizing enterocolitis
            - Esophageal atresia (with or without tracheoesophageal fistula)
            - Documented hyperglycemia
    - **EMLA/ LMX-4**
        - EMLA has demonstrated effectiveness for certain types of procedural pain, such as venipuncture, lumbar puncture, or immunizations.
        - Unfortunately, EMLA has not been effective in providing pain relief for heel pricks because of increased skin thickness
        - Dosing
            - GA ≥30 weeks to <37 weeks: Limited data available: Topical: 0.5 g per site and cover with an occlusive dressing for usual duration of application of 30 minutes prior to procedure.
                - One study of 30 preterm neonates (GA: ≥30 weeks) showed application to the heel for 1 hour resulted in no measurable changes in methemoglobin levels
                - Monitor patients closely with use
            - GA ≥37 weeks and weighing <5 kg: Topical: Apply ≤1 g per site and cover with an occlusive dressing for usual duration of application of 30 minutes prior to procedure.
            - Contraindications:
                - Patient has an allergy to lidocaine
                - Patient has liver disease, G6PD deficiency or idiopathic methemoglobinemia
                - Finger or heel sticks, as it can cause vasoconstriction
        - The vein can vasoconstrict after application, but a warm compress can reverse the vasoconstriction

- **Lidocaine Injection**
  - Lidocaine inhibits axonal transmission by blocking sodium channels
  - Typically, solutions with concentration <2% should be used
  - Dosing
    - Usual Dose: 1 - 2 mg/kg/dose (0.1 - 0.2 mL/kg/dose of a 1% solution)
    - Max dose: 5 mg/kg/dose (0.5 mL/kg/dose of a 1% solution)
- **Acetaminophen**
  - Acetaminophen acts by inhibiting the COX enzymes in the brain and has been well studied in neonates
  - Acetaminophen may be a good option for treatment of acute or procedural pain
  - Can be administered either orally or rectally
  - Dosing
    - PMA <32 weeks:
      - Oral: 12-15 mg/kg/dose Q12H
      - Rectal: 12-18 mg/kg/dose Q12h
    - PMA ≥32 weeks:
      - Oral: 12-15 mg/kg/dose Q8H
      - Rectal: 12-18 mg/kg/dose Q8h
    - Term:
      - Oral: 12-15 mg/kg/dose Q6H
      - Rectal: 12-18 mg/kg/dose Q6h
- **Opioid analgesics**
  - Medications such as Morphine or Fentanyl may be given to patients for procedural pain associated with invasive procedures, such as chest tube placement.
  - Caution should be used when providing narcotics or sedatives to any infant without a secure airway.
  - In many cases, non-pharmacologic interventions and/or oral sucrose will provide adequate pain relief; if opioids are needed, use the lowest effective dose.
  - Dosing:
    - Morphine:
      - IV, IM or SubQ: 0.05 mg/kg/dose
      - Oral: 0.1 mg/kg/dose
    - Fentanyl:
      - IV: 0.5 mcg/kg/dose
  - **To maintain minimal sedation, doses cannot be administered any sooner than every 30 minutes.**
    - **If more frequent dosing is needed, please follow the procedure for moderate sedation.**
- Procedure Specific Interventions
  - All non-pharmacologic interventions should be done prior to initiation of pharmacologic interventions and continued during and after procedure (see non-pharmacologic section)

Procedure	Interventions		
	1st Line	**2nd Line**	**3rd Line**
Circumcision	Sucrose and Lidocaine (EMLA and/or Injectable)		
Lumbar Puncture	Sucrose	EMLA (≥30 weeks)	
Heel stick Venipuncture Arterial stick	Sucrose	EMLA (≥30 weeks)	
PICC placement	Sucrose	Morphine	
PAL placement	Sucrose	EMLA (≥30 weeks)	
Chest tube	Injectable Lidocaine	Morphine	
Bladder tap	Sucrose	EMLA (≥30 weeks)	Morphine

Immunizations	Sucrose	EMLA (≥30 weeks)	
ROP exam	Sucrose and tetracaine		
Foley placement	Sucrose		
Tape removal Dressing change	Sucrose/saturation with sterile water	Acetaminophen	
Wound Vac Change	Sucrose	Acetaminophen	Morphine

*** If patient is <30 weeks gestation, skip EMLA and move to the next line of therapy**
*** If patient is < 27 weeks gestation or > 4 months of age, skip sucrose and move to the next line of therapy**

- Acute Neonatal Pain
  - Causes
    - Fracture
      - Usually respond well to non-pharmacologic interventions and immobilization
      - Acetaminophen can be used sparingly
    - Necrotizing Enterocolitis
      - Utilize NPASS scores and individualize therapy
    - Post-operative pain
      - IV Tylenol should be scheduled as first line
      - At JHACH, an order may be placed for no more than 24 hours and up to 4 doses of IV acetaminophen if patients meet one of the following:
        - NPO and no enteral medications administered or ordered in last 24 hours
        - NPO and surgery within the last 24 hours

For perioperative patients receiving acetaminophen, oral administration is encouraged. One dose of perioperative

        - (preoperative, intraoperative, or PACU) IV acetaminophen is allowed.
        - Severe mucositis Grade 3 or 4
      - A new order may be placed if patients continue to meet criteria after 24 hours.

- Post-operative Pain Management
  - There will be a collaborative approach to the post-operative pain management between Neonatology and the respective surgical team.
  - All neonates will receive optimal pain medication in the operating room, which may include local anesthesia in addition to opioids.
  - Neonatology and the surgery team should have post-operative communication regarding the specific surgical procedure with a general categorization as minor, moderate, or major procedure.
    - If the patient is going for a tracheostomy, please follow the post-op care found in the "Tracheostomy related care for patients in the NICU" Clinical Pathway.
    - If the patient is going for a surgical g-tube, please follow the post-op care found in the "Post-op G-tube bundle".
  - ***Ensure pain management plan is in place and plan has been discussed with family.***
  - All neonates should receive scheduled Acetaminophen IV, PO, or PR for 24 hours following surgery unless specific contraindication exists. The route of administration should be discussed with the surgical team prior to prescribing.
    - If a major procedure, continue scheduled Tylenol for minimum of 72 hours. Add Morphine OR Fentanyl scheduled.
      - Choose one of the dosing regimens below
        - Fentanyl Scheduled 0.5 mcg/kg Q3-4H
        - Morphine Scheduled 0.05 mg/kg Q3-4H
      - For continued pain scores ≥4, maximize dosing and frequency of selected agent
        - Choose one of the dosing regimens below
          - Fentanyl 0.5 mcg/kg/hr
          - Morphine 0.1 mg/kg/hr
    - If a moderate procedure, then continue scheduled Tylenol for minimum of 48 hours

- For pain scores ≥4, add one of the following
    - Fentanyl 0.5 mcg/kg Q3-4HPRN
    - Morphine 0.05 mg/kg Q3-4HPRN
- If a minor procedure, continue scheduled Tylenol for minimum of 24 hours

- Acute on Chronic Neonatal Pain
    - Causes
        - Mechanical ventilation
        - Significant hydrocephalus/increased ICP
        - Fractures due to osteopenia
        - Severe muscle spasticity
    - Treatment
        - See the algorithm below
    - Continuous Infusion Drips
        - Drips are sometimes appropriate when PRN medications must be given frequently, as multiple IV-line breaks can increase the risk of infection
        - Medications should be initiated as PRN doses to prevent overuse and over sedation

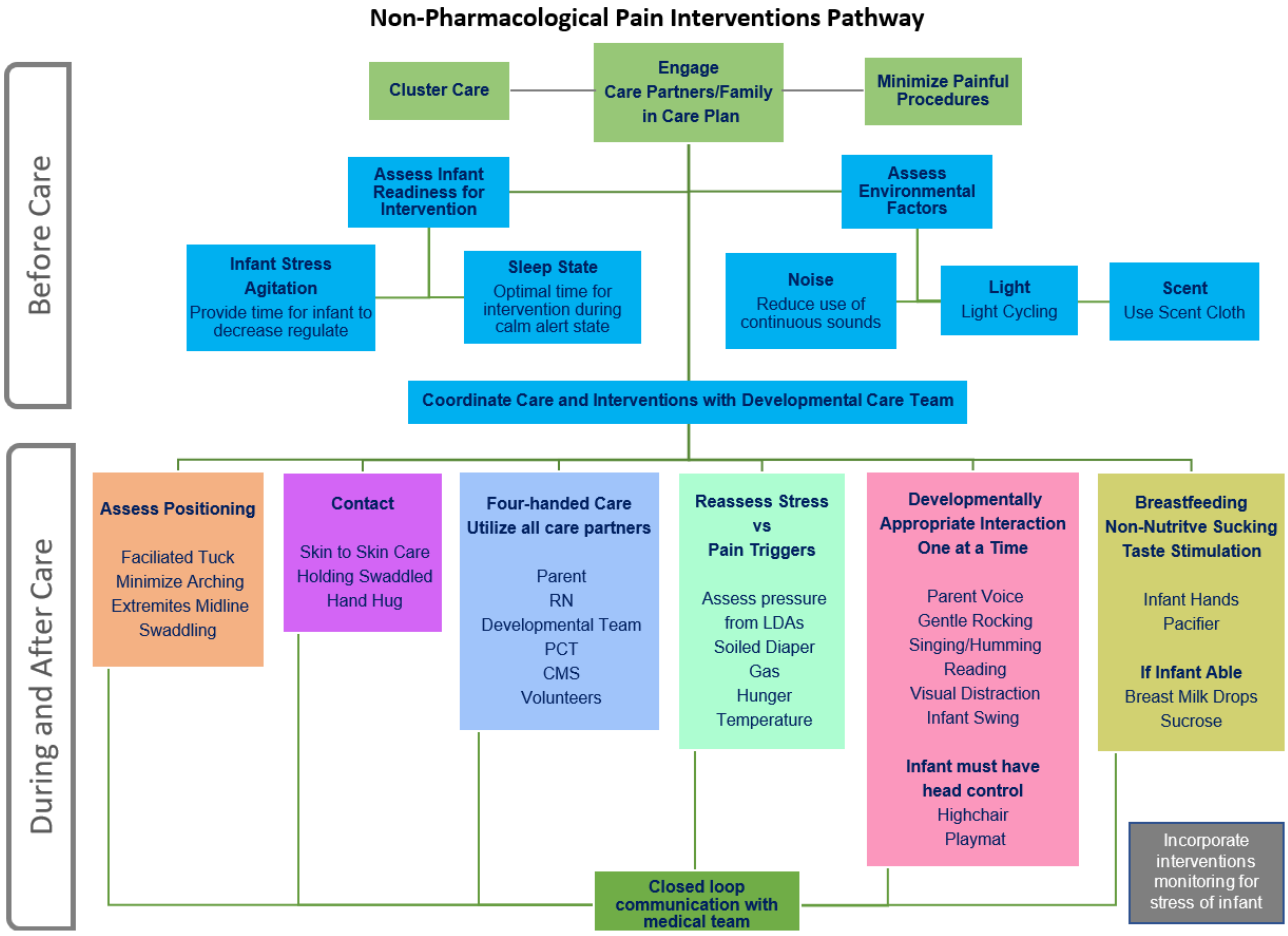
- Medications
    - General Information
        - Long-term use of opioids and benzodiazepines in neonates can lead to prolonged mechanical ventilation and delay in the passage of meconium and carries an inherent risk for tolerance and withdrawal, necessitating prolonged dose taper regimens.
        - There is recent evidence of an increase in severe neurological morbidity with these medications.
    - **Opioids**
        - Treatment with opioids does not have a significant positive effect with respect to neonatal mortality, duration of ventilation, short-term or long-term neurodevelopmental outcomes, incidence of severe intraventricular hemorrhage, any IVH, nor periventricular leukomalacia.
        - Opioid exposure is associated with
            - Longer courses of mechanical ventilation, hypotension, pharmacologic withdrawal, urinary retention, decreased intestinal motility, NEC, severe BPD, longer length of stay, lower cognition, and lower motor and language development scores at 2 years of age
        - Opioid tolerance can develop after 7-10 days of exposure, requiring dose escalation during pain treatment followed by gradual dose tapering to avoid physiologic withdrawal
            - If a patient is on opioids for ≥ 7 days, the patient should be monitored for withdrawal
        - **Fentanyl**
            - Is 50–100 times more potent than Morphine
            - A single dose of Fentanyl given to ventilated preterm newborns significantly reduces pain behaviors and changes in heart rate; it also increases growth hormone levels.
            - Continuous infusions decrease the neuroendocrine stress response, but boluses increase the duration of mechanical ventilation and a trend toward a longer time to full enteral feeds.
            - **Studies show that exposure to a continuous infusion for 1 week was associated with neurodevelopmental impairment at 24 months corrected age**
            - Given the above information, Fentanyl should always be initiated with PRN dosing, then moved to scheduled doses if needed. Continuous infusions should be limited to <1 week.
            - Dosing:
                - Intermittent dosing: 0.5 - 3 mcg/kg/dose Q2-4 hours IV
                - Continuous Drip: 0.5 - 3 mcg/kg/hr
        - **Morphine**
            - Mean onset of action is 5 minutes, and the peak effect is at 15 minutes
            - Routine Morphine infusion in preterm newborns who received ventilatory support neither improved pain relief nor protected against poor neurologic outcome

- Neonates are at greater risk for opioid-associated respiratory depression because of their immature respiratory center responses to hypoxia and hypercarbia
- 2021 update to the Cochrane review concluded that there is uncertainty whether opioids have any effect on reducing pain in mechanically ventilated infants
- Dosing:
    - Intermittent dosing: 0.05 - 0.2 mg/kg/dose Q3-4 hours IV, IM, or SubQ
    - Continuous Drip: 0.01 - 0.2 mg/kg/hr

- **Alpha-2 agonists**
    - **Dexmedetomidine**
        - Highly selective, centrally acting α_2 adrenergic agonist
        - Mechanism of action:
            - Activation of α_2 adrenergic receptors in the medullary vasomotor center leads to a reduction in norepinephrine turnover and sympathetic nervous system signaling from the locus coeruleus, leading to increased endogenous GABAergic activity, which causes sedation.
            - Stimulates the release of substance P from the dorsal horn of the spinal cord leading to analgesia and can potentiate the effects of opioids.
        - Stimulates the natural sleep pathways and induces activity similar to non-rapid eye movement sleep in adults and children.
        - The effects in the airway and respiratory system also mimic natural sleep and therefore maintain spontaneous breathing and upper airway tone.
            - It is postulated that its use should enable quicker weaning off mechanical ventilation and support extu Require moderate sedation for a procedure or pre-op
        - Dosing
            - Dosing for neonates with corrected gestational age 28-36 weeks:
                - Loading dose: 0.1 mcg/kg IV over 10 minutes
                - Maintenance infusion:
                    - Start at 0.1 mcg/kg/hr
                    - Titrate up by 0.1 mcg/kg/hr q12 hours as needed
                - Max infusion rate: 1.5 mcg/kg/hr
                - PRN boluses: Not recommended due to hypotension associated with bolus
            - Dosing for neonates with corrected gestational age > 36 weeks:
                - Loading dose: 0.3 mcg/kg IV over 10 minutes
                - Maintenance infusion:
                    - Start at 0.3 mcg/kg/hr IV
                    - Titrate up by 0.1 mcg/kg/hr IV q6 hours as needed
                - Max infusion rate: 2.5 mcg/kg/hr IV
            - PRN boluses: 0.25-1 mcg/kg/dose IV
            - **<u>Note maximum dose difference based on gestational age</u>**
    - **Clonidine**
        - Mechanism of action:
            - A centrally acting α_2 selective adrenergic agonist.
            - Stimulates the pre-synaptic α_2 adrenoceptors of the locus ceruleus, decreasing norepinephrine release.
        - Has also shown action in cholinergic, purinergic, and serotonergic pathways, resulting in analgesia.
        - May exert neuroprotective effects by preventing apoptosis induced by anesthesia.
        - Reduces such noradrenergic activity, thus reversing the cause of opioid withdrawal.
        - Does not cause oversedation and respiratory depression and usually does not require a taper.
        - Can cause hypotension and bradycardia, but the doses that were used in clinical trials were not associated with significant differences in the incidence of these adverse effects in the treatment group compared with the control group.

        - Dosing
            - Dosing: 0.5-2 mcg/kg/dose Q3-6H PO
- **Benzodiazepines**
    - Continuous infusion of midazolam has been shown to produce significantly lower sedation scores and lower cognitive scores that correlate with cumulative benzodiazepine dose exposure.
    - Main complications include myoclonic jerking, excessive sedation, respiratory depression, and occasional hypotension.
    - Midazolam
        - Preterm neonates are at a high risk of transient hypotension and decreased mean cerebral blood flow after bolus doses of Midazolam
            - NOPAIN trial demonstrated **an unacceptable risk of severe IVH, PVLM, or death in preterm neonates who received midazolam in any form.**
            - Was associated with worse short-term adverse effects compared to Morphine alone
        - A recent review found no apparent clinical benefit of midazolam compared to opiates in mechanically ventilated neonates
        - The elimination of midazolam is reduced in newborn infants and results in an increase in the serum levels
        - Dosing:
            - Intermittent dosing: 0.05 to 0.15 mg/kg/dose Q2-4 hours IV or IM
            - Continuous drip: 0.01 to 0.4 mcg/kg/hr
            - Intranasal: 0.2 to 0.3 mg/kg/dose
- **Gabapentin**
    - A gamma-aminobutyric acid analog, that is thought to inhibit pain via voltage-dependent calcium ion channels in the central nervous system.
    - Has been used to treat neuropathic pain related to visceral hyperalgesia in the neonatal population.
    - Has a mild reported side effect profile and apparent lack of drug-drug interactions due to its renal route of excretion.
    - Symptom relief for chronic irritability and feeding intolerance occurred in both populations, as was a reduction in the use of opioids and benzodiazepines.
    - Option for the management of refractory pain and agitation in pediatrics as it is highly lipophilic, hence, penetrates well through the blood-brain barrier
    - Decreases the mean number of other neuro-sedative medications from 2.5 per day at the start of therapy to 1.7 per day after 14 days of gabapentin.
    - The use of gabapentin in medically complex neonates and infants was associated with a reduction in pain scores and the need for multiple neuro-sedative medications.
        - Might be a good option for patients with chronic BPD or patients with severe IVH
    - Dosing
        - Dosing: 2.5-10 mg/kg/day divided every 8 hours
        - Increase dose every 2-3 days to reach the desired effect
        - Maximum dose is 35 mg/kg/day

Neonatal Pain Management Algorithm / Pathway



Treatment of Procedural Pain

- All non-pharmacologic interventions should be performed prior to initiation of pharmacologic interventions, and continued during and after procedure (see non-pharmacologic section)

Procedure	Interventions		
	1st Line	2nd Line	3rd Line
Circumcision	Sucrose and Lidocaine (EMLA and/or Injectable)		
Lumbar Puncture	Sucrose	EMLA (≥30 weeks)	
Heel stick Venipuncture Arterial stick	Sucrose	EMLA (≥30 weeks)	
PICC placement	Sucrose	Morphine	
PAL placement	Sucrose	EMLA (≥30 weeks)	
Chest tube	Injectable Lidocaine	Morphine	
Bladder tap	Sucrose	EMLA (≥30 weeks)	Morphine
Immunizations	Sucrose	EMLA (≥30 weeks)	
ROP exam	Sucrose and tetracaine		
Foley placement	Sucrose		
Tape removal Dressing change	Sucrose/saturation with sterile water	Acetaminophen	
Wound Vac Change	Sucrose	Acetaminophen	Morphine

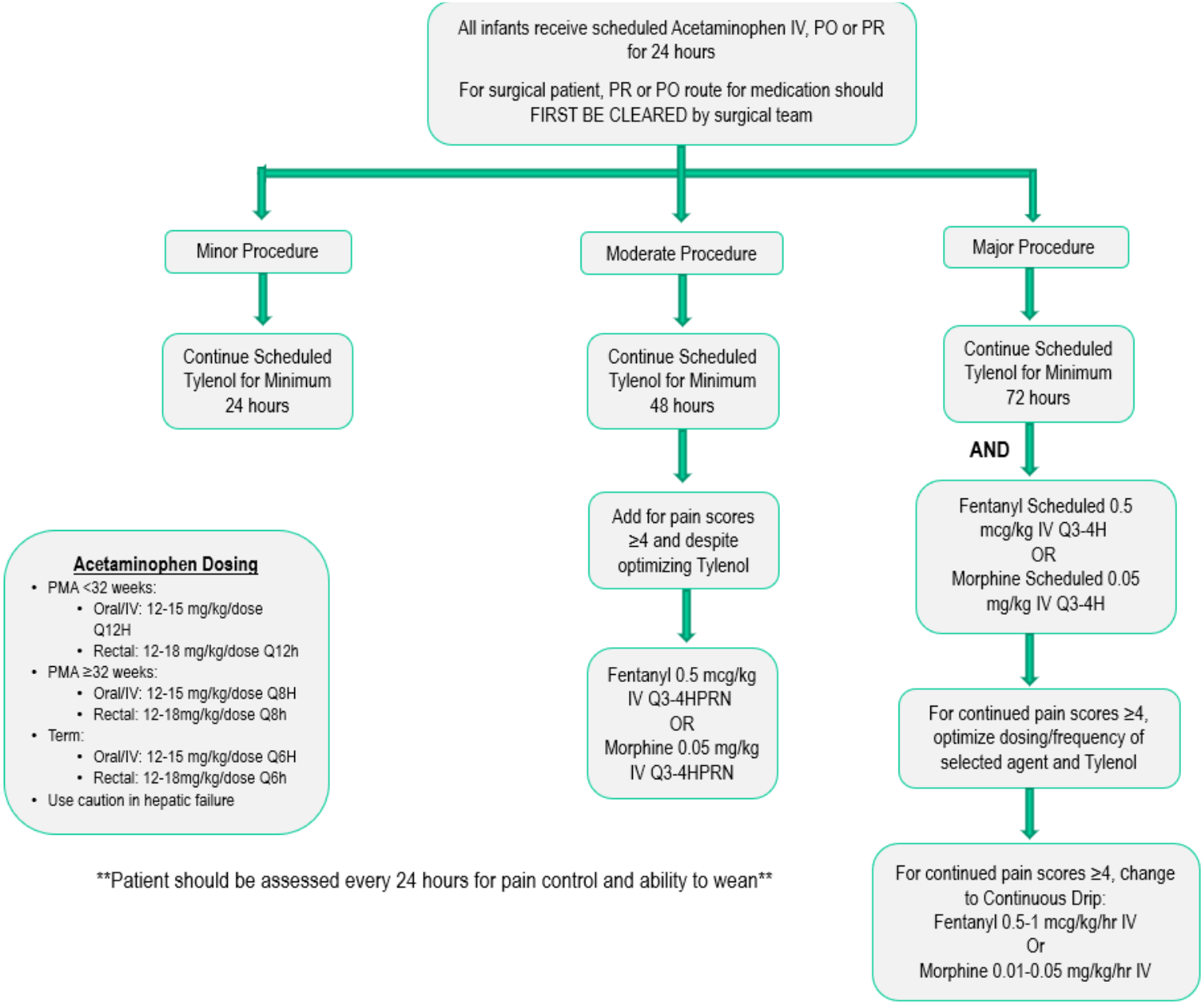
*** If patient is <30 weeks' gestation, skip EMLA and move to next line therapy**

*** If patient is < 27 weeks gestation or > 4 months of age, skip sucrose and move to the next line of therapy**

- Oral Sucrose
  - Do not use in pts >4 months of age
  - Max doses per administration:
    - GA 27 to 31 weeks: 0.5 mL
    - GA 32-36 weeks: 1 mL
    - GA ≥37 weeks: 2 mL
  - Contraindications
    - Patients with irritability or for ongoing pain relief, Known, suspected, or at high risk for necrotizing enterocolitis, Esophageal atresia (with or without tracheoesophageal fistula), Documented hyperglycemia
- EMLA/ LMX-4
  - GA ≥30 weeks to <37 weeks: 0.5 g per site and cover for 30 minutes prior to procedure
  - GA ≥37 weeks: ≤1 g per site and cover for 30 minutes prior to procedure
- Lidocaine
  - Usual Dose: 1 – 2 mg/kg/dose (0.1 – 0.2 mL/kg/dose of a 1% solution)
  - Max dose: 5 mg/kg/dose (0.5 mL/kg/dose of a 1% solution)
- Acetaminophen
  - PMA <32 weeks:
    - Oral: 12-15 mg/kg/dose Q12H
    - Rectal: 12-18 mg/kg/dose Q12h
  - PMA ≥32 weeks:
    - Oral: 12-15 mg/kg/dose Q8H
    - Rectal: 12-18 mg/kg/dose Q8h
  - Term:
    - Oral: 12-15 mg/kg/dose Q6H
    - Rectal: 12-18 mg/kg/dose Q6h
- Morphine:
  - IV, IM or SubQ: 0.05 mg/kg/dose
  - Oral: 0.1 mg/kg/dose
  - Doses are for opiate naïve patients
- Fentanyl:
  - IV: 0.5 mcg/kg/dose
  - Administer over 5-10 minutes
  - Doses are for opiate naïve patients
- **To maintain minimal sedation, doses cannot be administered any sooner than every 30 minutes.**
  - **If more frequent dosing is needed, please follow the procedure for moderate sedation.**

Treatment of Post-Operative Pain

If the patient is going for a tracheostomy or surgical G-tube, please follow the post-op care found in the "Tracheostomy related care for patients in the NICU" Clinical Pathway or the "Post-op G-tube bundle" respectively

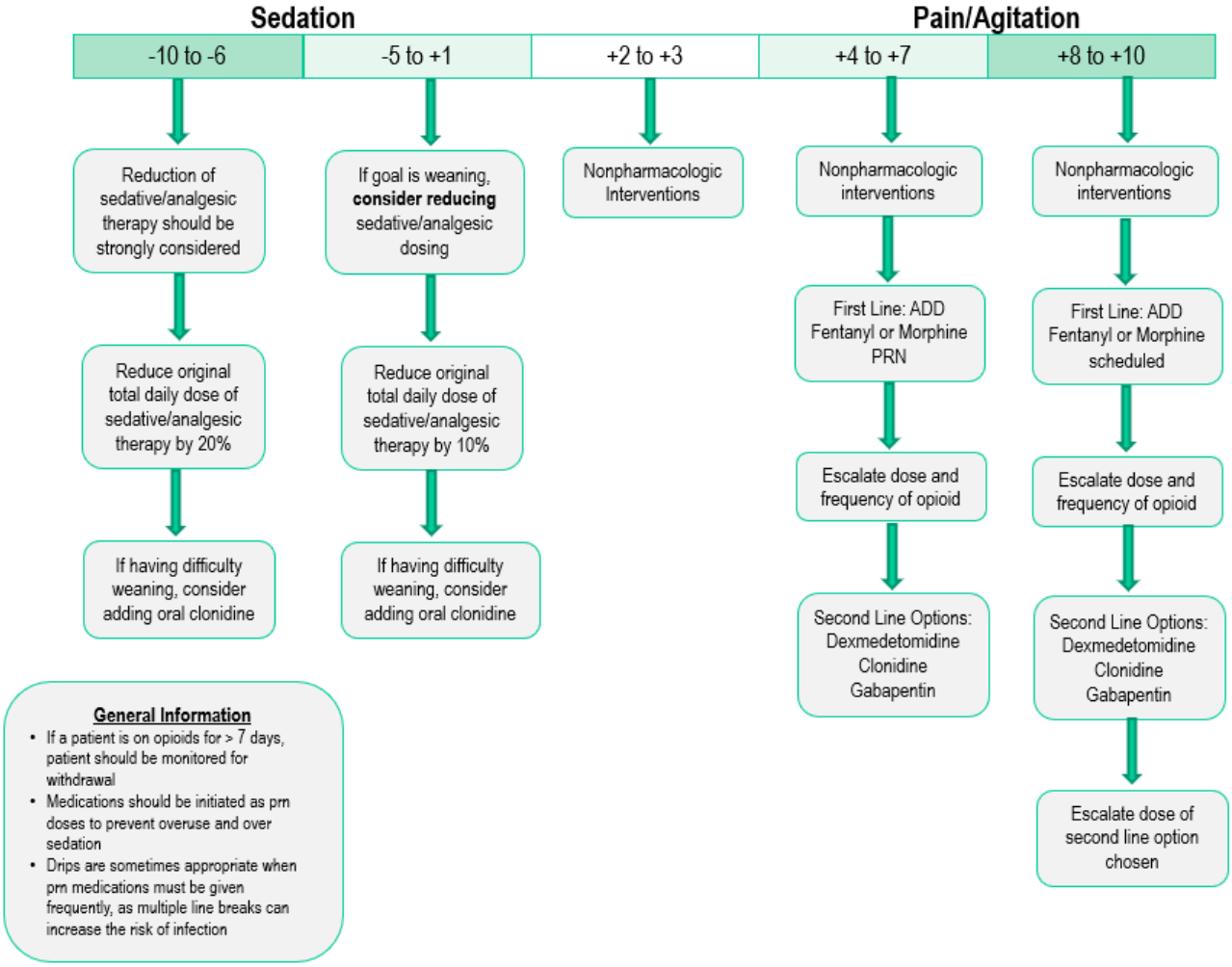


Surgeries Listed by Degree of Severity

Minor Anticipated duration of pain= ~24-48 hours	**Moderate** Anticipated duration of pain= ~72 hours	**Major** Anticipated duration of pain= ~96 hours
Bronchoscopy	Gastrostomy tube placement	Combined open procedures in multiple parts of the body
Central line placement	Laparoscopic procedures (Including Nissen fundoplication, and/or combined laparoscopic procedures in multiple parts of the body)	Esophageal atresia repair
Chest tube placement	Myelomeningocele repair	Exploratory laparotomy (With bowel resection, creation of stomas, and extensive adhesiolysis)
Circumcision	Open inguinal hernia repair	Median Sternotomy
Laparoscopic inguinal hernia repair	Peritoneal dialysis catheter insertion	Open Nissen fundoplication
Reservoir	Thoracoscopic procedures with chest tube placement	Thoracotomy
Thoracoscopic procedures without chest tube placement	Ventriculoperioneal shunt	
Ventriculosubgaleal shunt		

Treatment of Acute on Chronic Pain

If patient is ≥6 months or has difficult pain control, consider consulting the pain team



- Medication Dosing
  - Fentanyl
    - Intermittent dosing: 0.5 - 3 mcg/kg/dose Q2-4 hours IV
      - Administer over 5-10 min
    - Continuous Drip: 0.5 - 3 mcg/kg/hr
  - Morphine
    - Intermittent dosing: 0.05 - 0.2 mg/kg/dose Q3-4 hours IV, IM, or SubQ
    - Continuous drip: 0.01 - 0.2 mg/kg/hr
  - Dexmedetomidine
    - Neonates with corrected gestational age 28-36 weeks:
      - Loading dose: 0.1 mcg/kg IV over 10 minutes
      - Maintenance infusion: Start at 0.1 mcg/kg/hr
    - Neonates with corrected gestational age > 36 weeks:
      - Loading dose: 0.3 mcg/kg IV over 10 minutes
      - Maintenance infusion: Start at 0.3 mcg/kg/hr IV
  - Clonidine
    - Oral: 0.5-2 mcg/kg/dose Q3-6H
  - Midazolam
    - Intermittent dosing: 0.05 to 0.15 mg/kg/dose Q2-4 hours IV or IM
    - Continuous Drip: 0.01 to 0.4 mcg/kg/hr
    - Intranasal: 0.2 to 0.3 mg/kg/dose
  - Gabapentin
    - Oral: 2.5-10 mg/kg/day divided every 8 hours
    - Increase dose every 2-3 days to reach desired effect

Maximum dose is 35 mg/kg/day

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